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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/509,648	10/05/2000	Mark F. Charette	CIBT-P01-569	7787

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EXAMINER	
BUNNER, BRIDGET E	
ART UNIT	PAPER NUMBER
1647	17

DATE MAILED: 11/06/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No.	Applicant(s)	
	09/509,648	CHARETTE ET AL.	
	Examin r	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *13-15,20,21 and 27-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,16-19 and 22-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-32* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 05 August 2002 (Paper No. 15) has been entered in full. Claims 9 and 21 are amended.

Election/Restrictions

Applicant's election with traverse of the species, cytokine antagonist and retinoid receptor, in Paper No. 15 (05 August 2002) is acknowledged. The traversal is on the ground(s) that the species at least partially overlap with one another, and therefore, such delimitation of species does not comply with MPEP 806.04(f). Applicant argues that the term "cytokine antagonist" (species a) encompasses such molecules as cytokine binding proteins and cytokine receptor binding proteins. Applicant asserts that cytokine binding proteins are also "molecules that bind an endogenous ligand" (species b), thus the scope of species a and b overlap. This is not found persuasive. The Examiner acknowledges that a cytokine antagonist may encompass binding proteins and receptor binding proteins that bind an endogenous ligand. However, the species requirements set forth in the previous Office Action are for (1) a molecule that overcomes morphogen inhibition and (2) a receptor for an endogenous ligand that a molecule binds. These species of molecule and receptor are separate and do not overlap with one another. It is noted that Applicant indicates Applicant is entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141 (MPEP 809.02(a)).

Furthermore, Applicant indicates that claims 13-15 are drawn to a non-elected species belonging to a Markush group and that "if members of the Markush group are sufficiently few in

number or so closely related that a search and examination of the entire claim can be made without serious burden, the examiner must examine all claims..." (MPEP 803.02). This is not found persuasive. An art search for the molecules recited in claim 9 that overcome morphogen inhibition would not overlap since each molecule is unique, requiring a unique search of the prior art. Searching all of the species in a single patent application would provide an undue search burden on the Examiner and the USPTO's resources because of the non-coextensive nature of these searches.

The requirement is still deemed proper and is therefore made FINAL.

Claims 13-15, 20-21, and 27-32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species and group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 13 (18 April 2002) and Paper No. 15 (05 August 2002).

Claims 1-12, 16-19, and 22-26 are under consideration in the instant application. The claims also read upon the following species: Alzheimer's disease from the disorder group, cytokine antagonist from the agent capable of releasing morphogen activity group, 2-p-bromocinnamylaminoethyl)-isoquinolinesulfonamide from the protein kinase A inhibitor group, SEQ ID NO: 2 from the morphogen amino acid sequence group, OP-1 from the morphogen group, and retinoid receptor from the molecule that binds an endogenous ligand group

Specification

1. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

2. The disclosure is objected to because of the following informalities:

2a. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

2b. Patent applications are referenced throughout the disclosure (pg 1, lines 14-15; pg 21, lines 8-9; pg 25, line 25; pg 35, line 11). The status of the applications must be updated.

Appropriate correction is required.

Claim Objections

3. Claims 8-9, 11, 16-17, 19, 26 are objected to because of the following informalities.

3a. Claims 8-9, 16-17, 19, and 26 recite non-elected species.

3b. The acronym "CTNF" in claim 11 should be "CNTF".

Appropriate correction is required.

35 USC § 112, first paragraph

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-12, 16-19, and 22-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing leukemia inhibitory factor (LIF)-induced dendritic retraction comprising adding an antibody to gp130 to sympathetic neurons *in vitro* that have been treated with LIF and osteogenic protein-1 (OP-1) and wherein said antibody reduces LIF-induced dendritic retraction, does not reasonably provide enablement for a method for potentiating morphogen activity, a method for promoting neuronal cell growth, a method for treating a disorder characterized by neuronal cell loss, or a method for treating a

neurodegenerative disorder comprising administering to a mammal a composition comprising a molecule that overcomes morphogen inhibition. Additionally, the specification is enabling for a method of reducing ciliary neurotrophic factor (CNTF)-induced dendritic retraction comprising adding phosphatidylinositol-specific phospholipase C (PI-PLC) to sympathetic neurons *in vitro* before the neurons have been treated with CNTF and osteogenic protein-1 (OP-1) and wherein said PI-PLC reduces CNTF-induced dendritic retraction. The specification is also enabling for a method of reducing the inhibitory effects of LIF on OP-1 stimulated dendritic growth comprising adding an anti-LIF antibody to sympathetic neurons *in vitro* that have been treated with LIF and OP-1 and wherein said antibody reduces the inhibition of LIF on OP-1 stimulated dendritic growth. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-12, 16-19, and 22-26 are directed to a method for potentiating morphogen activity, a method for promoting neuronal cell growth, a method for treating a disorder characterized by neuronal cell loss, and a method for treating a neurodegenerative disorder comprising administering to a mammal a composition comprising a molecule that overcomes morphogen inhibition. The claims recite that the morphogen activity is endogenous or the result of an exogenously provided morphogen. The claims also recite that the molecule that overcomes morphogen inhibition is a cytokine antagonist, more specifically a neuropoetic cytokine antagonist. The claims recite that the neuropoetic antagonist is a LIF antagonist or a CNTF antagonist. The claims also recite that the morphogen comprises an amino acid sequence having at least 70% homology with the C-terminal seven-cysteine skeleton of human OP-1, residues

330-431 of SEQ ID NO: 2. The claims recite that the molecule binds an endogenous ligand for a retinoid receptor. The claims are directed to a molecule that is a cAMP-dependent messenger pathway inhibitor, specifically a protein kinase A inhibitor ((2-p-bromocinnamylaminoethyl)-isoquinolinesulfonamide).

The specification teaches that LIF inhibits dendritic growth in cultured sympathetic neurons (pg 32, line 25). The specification teaches that the inhibitory effects of LIF on OP-1-induced dendritic growth is substantially reduced when 10-30 μg/ml of a polyclonal anti-LIF antibody is added to the medium (pg 27, lines 25-27; Figure 5). The specification also discloses that cultures of sympathetic neurons are treated with OP-1 for 5 days to induce dendritic growth and then LIF, antibody to gp130, or both agents are added on the 6^{th} day (pg 33, lines 1-10). The specification teaches that the antibody to the gp130 protein reduces the response to LIF (pg 33, Table III). Additionally, the specification discloses that cultures of sympathetic neurons are exposed to OP-1, OP-1 and CNTF, or OP-1 and LIF. The specification also teaches that some cultures are treated with PI-PLC before the CNTF and LIF treatments (pg 34, lines 1-6). The specification teaches that the CNTF-induced dendritic retraction is reduced by prior PI-PLC treatment (pg 33, lines 23-25; Figure 9). However, the specification of the instant application does not teach any methods or working examples that administer any molecule to a mammal and overcome morphogen inhibition to potentiate morphogen activity, promote neuronal cell growth, treat a disorder characterized by neuronal cell loss, or treat a neurodegenerative disorder. The specification does not disclose administering any molecules to a mammal that are cAMP-dependent messenger pathway inhibitors. Undue experimentation would be required of the

skilled artisan to determine the route of administration of all possible molecules, as well as the quantity and duration of treatment.

The specification at pages 2 and 22-24 outline a prophetic procedure for administering to a mammal a molecule capable of releasing inhibition on morphogen activity. However, this is not adequate guidance, but is merely an invitation for the artisan to use the current invention as a starting point for further experimentation. Furthermore, the claimed method may not necessarily overcome morphogen inhibition to potentiate morphogen activity, promote neuronal cell growth, treat a disorder characterized by neuronal cell loss, or treat a neurodegenerative disorder. The skilled artisan must resort to trial and error experimentation to determine the optimal dosage, duration, and mode of administration of all possible molecules. Such trial and error experimentation is considered undue. According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed."

Due to the large quantity of experimentation necessary to potentiate morphogen activity, promote neuronal cell growth, treat a disorder characterized by neuronal cell loss, and treat a neurodegenerative disorder and to determine the optimal dosage, duration, and mode of administration of all possible molecules, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the unpredictability of the effects of administering a molecule to a mammal, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

6. Claim 17 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 17 recites a method of treating a neurodegenerative disorder comprising administering to a mammal a composition comprising a molecule that overcomes morphogen inhibition wheren the composition further comprises a morphogen and the morphogen is human OP-1, mouse OP-1, human OP-2, mouse OP-2, 60A, GDF-1, BNT2A, BMT2B, DPP, Vgl, Vgr-1, BNW3, BNW5, or BW6.

The specification as originally filed does not provide adequate written description for morphogens BNT2A, BMT2B, BNW3, BNW5, or BNW6. It is not expressly asserted, nor does it flow naturally from the specification. (It is noted to Applicant that this issue could be overcome by amending the claim to recite BMP2A, BMP2B, BMP3, BMP5, and BMP6.)

35 USC § 112, second paragraph

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-12, 16-19, and 22-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claims 1-12, 16-19, and 22-26 are indefinite because the claims do not have a step that clearly relates back to the preamble. For example, there is no step indicating how administration of a molecule potentiates morphogen activity. There is no step indicating how administration of

a molecule promotes neuronal cell growth, treats a disorder characterized by neuronal cell loss, or treats a neurodegenerative disorder.

10. The term "morphogen activity" in claims 1-12, 16-19, and 22-26 is a relative term which renders the claims indefinite. The term "morphogen activity" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It cannot be determined if "morphogen activity" means for example, inducing the migration, proliferation and differentiation of progenitor cells, inducing bone morphogenesis, or repairing non-chondrogenic tissues.

11. The term "morphogen inhibition" in claims 1-12, 16-19, and 22-26 is a relative term which renders the claims indefinite. The term "morphogen inhibition" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It cannot be determined if "morphogen inhibition" means for example, inhibiting the migration, proliferation and differentiation of progenitor cells, inhibiting bone morphogenesis, or inhibiting the repair of non-chondrogenic tissues.

12. Regarding claims 11-12, 16-18, and 24-26, the acronyms "LIF", "CNTF", "OP-1", "OPX", "OP-2", "GDF-1", "BNT2A", "BMT2B", "DPP", "Vgl", "Vgr-1", "BNW3", "BNW5", "BW6" renders the claims vague and indefinite. Abbreviations should be spelled out in all independent claims for clarity.

Conclusion

No claims are allowable.

The art made of record and not relied upon is considered pertinent to applicant's disclosure:

Ip et al. Annu Rev Neurosci 19 : 491-515, 1996.

Guo et al. Molec Biol Cell 6(S): 99a, 1995.

Guo et al. J Neurosci 19(6) : 2113-2121, 1999.

Guo et al. Develop Brain Res 104(1-2) : 101-110, 1997.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

BEB
Art Unit 1647
October 24, 2002